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Erythrocytapheresis Limits Iron Accumulation in Chronically Transfused Sickle Cell Patients

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Cerebrovascular accidents (CVA) as a complication of sickle cell disease occur most frequently in childhood. Life-long transfusion prevents recurrent stroke, but inevitably leads to iron overload. Although effective chelation exists, many patients are not compliant. Erythrocytapheresis, an automated method of red blood cell exchange, was evaluated as an alternative to control transfusion-related iron load. Eleven patients with sickle cell anemia and a history of stroke were converted from simple transfusion to pheresis. Total time on pheresis for the group averaged 19 months (range 4–36 months). No significant complications occurred with a mean pre-pheresis hemoglobin S (Hb S) level of 44%. Blood utilization increased by an average of 50%. The effect of pheresis on serum ferritin depended on the patient's pre-pheresis ferritin level and chelation regimen. Ferritin levels remained stable for chelated patients with ferritin levels ⩾5,000 ng/ml, but decreased in a chelated patient with a pre-pheresis ferritin level of 4,000 ng/ml. For non-chelated patients with significant pre-pheresis iron load, ferritin levels remained stable. No patient on chelation prior to pheresis was able to discontinue deferoxamine. However, one patient with pre-pheresis ferritin of 500 ng/ml maintained serum ferritin levels <200 ng/ml for 36 months of pheresis without chelation. Pheresis is more expensive than simple transfusion unless the cost of chelation and organ damage from iron overload are considered. Erythrocytapheresis is a safe method of controlling Hb S levels and limiting or preventing iron load in chronically transfused sickle cell patients. Am. J. Hematol. 59:28–35, 1998. © 1998 Wiley-Liss, Inc.

Key words: sickle cell disease; transfusion; erythrocytapheresis; chelation; iron

INTRODUCTION

Cerebrovascular complications are an important cause of morbidity in sickle cell disease. Cerebral infarction occurs primarily in pediatric patients with a peak incidence in the latter part of the first decade [1,2]. Although chronic transfusion is effective in preventing recurrent stroke [3], no safe endpoint to therapy is known. Patients have experienced recurrent stroke when transfusions were discontinued after as long as 12 years [4]; thus, current recommendations suggest that transfusion therapy continue indefinitely. Risks associated with a chronic transfusion program include alloimmunization, especially in a patient population which often receives ethnically mismatched blood [5]. Transmission of infectious agents still occurs [6], but most significant is the inevitable consequence of iron overload in chronically transfused patients [7]. Although deferoxamine provides effective chelation, its use is limited by expense, side effects, and poor compliance [8,9].

Erythrocytapheresis is a method of automated red blood cell exchange recently reported to be effective in stabilizing or reducing iron overload for chronically transfused sickle cell patients [10,11]. Both previous reports show erythrocytapheresis is safe and effective in preventing recurrent stroke. Erythrocytapheresis increased blood utilization, but iron load, as measured by serum ferritin, decreased in some cases significantly enough to allow discontinuation of deferoxamine in some patients. Based on these encouraging reports, we evaluated the use of erythrocytapheresis and its effect on blood utilization, complications, efficacy, cost, and iron load for chronically transfused sickle cell patients at our institution by analyzing periods of simple transfusion and pheresis in the same patient.

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TABLE I. Clinical Characteristics and Laboratory Values*

				Simple transfusion						Pheresis					
Patient	Age (years)	Sex	Chelation	Total duration (years)	Observation period (years)	Visit interval (days)	Hb	Hb S	Retic	Total duration (years)	Observation period (years)	Visit interval (days)	Hb	Hb S	Retic
1	22.2	M	Yes	14.2	1.0	21.6	10.2	43.4	9.1	2.4	1.6	32.7	10.4	55.9	9.7
2	16.3	M	Yes	10.0	1.0	28.5	9.8	39.0	8.8	1.1	1.1	36.1	9.9	39.1	11.6
3	23.5	F	Yes	14.3	1.0	35.0	9.8	20.5	6.2	1.1	1.1	43.3	9.5	32.0	8.0
4	19.1	M	Yes	12.5	1.0	26.7	9.4	42.7	11.6	2.1	1.6	31.6	9.5	51.4	12.9
5	16.7	M	Yes	8.2	1.0	37.1	8.4	28.8	8.2	1.1	1.1	33.7	8.5	29.1	10.3
6	25.3	M	Yes	13.3	1.0	22.0	10.9	41.0	6.0	2.0	1.5	29.1	10.6	52.2	8.7
7	11.2	F	Yes	4.7	1.0	35.7	9.3	18.8	6.9	0.3	0.3	39.7	8.9	28.7	8.7
8	20.8	F	No	0.3	0.3	37.7	11.1	57.5	7.6	3.1	1.5	34.3	11.9	51.6	7.1
9	12.8	F	No	0.1	—	—	—	—	—	1.2	1.2	33.9	9.8	48.1	11.5
10	20.3	M	No	2.2	1.0	23.6	9.8	32.3	8.8	2.3	1.6	35.9	9.6	41.0	12.6
11	18.2	M	No	5.5	1.0	28.3	10.6	52.4	10.0	0.8	0.3	35.7	12.0	50.3	11.4
									Average						
				7.7	0.9	29.6	9.9	37.6	8.3	1.6	1.2	35.1	10.1	43.6	10.2

*Hb, hemoglobin. Note: During the observation period, all phereses were performed in the same manner on a COBE® Spectra™ system. Standard deviation of the Hb S is ± 0.4%.

MATERIALS AND METHODS

Subjects

Eleven patients with sickle cell anemia and history of stroke were converted from a traditional simple/partial transfusion protocol to erythrocytapheresis. Informed consent was obtained from subjects or their parents. Seven of the 11 patients were males. Patient age ranged from 11 to 24 years. Older patients were initially selected due to extent of iron load as well as ease of venous access. (Younger patients are now started on the pheresis protocol. The smallest to date is an 18 kg six-year-old). Nine of the 11 patients were on a simple transfusion program for greater than two years prior to pheresis (mean of eight years). For the group to date, total time on pheresis averages 19 months with a range of four to 36 months. Chelation with deferoxamine was continued in the seven patients using the medication prior to the switch to pheresis. Of the non-chelated patients, three had not yet required chelation, and one could not use deferoxamine due to allergy.

Erythrocytapheresis Protocol

Phereses were performed on a COBE® (Lakewood, CO) Spectra™ continuous-flow system that removes whole blood from the patient and returns patient plasma and donor packed red blood cells (PRBCs). PRBCs were sickle negative, leukoreduced, and phenotypically matched for each patient (C, E, K, Fy^a, and Jkb for our patients). Only CPDA-1 PRBCs were used, and the hematocrit of each unit was determined prior to pheresis.

An 18-gauge apheresis needle placed in the antecubital area was used for outflow and a 19–20 gauge angiocatheter was used for inflow. The COBE system calculates exchange volume with input of patient height, weight, initial hematocrit, hematocrit of replacement PRBCs, desired final hematocrit, and the fraction of cells remaining (degree of exchange) for each procedure. The original goals of the protocol were to maintain an average pre-pheresis hemoglobin S (Hb S) $\leqslant$50% and a post-pheresis hematocrit of 35%. Patients required pheresis an average of every 35 days.

Patients had red blood cell (RBC) phenotype determined prior to starting chronic transfusion. (Phenotype determination included testing for the five major Rh antigens.) All patients are monitored for development of alloantibodies with direct and indirect Coombs' test prior to each pheresis. Annual infectious disease testing includes hepatitis B studies (core antibody, surface antibody, and surface antigen), hepatitis C antibody and human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay (ELISA). Serum ferritin levels are obtained at the time of each pheresis using an immunoassay from Chiron Diagnostics (Walpole, MA). Pre- and post-pheresis complete blood counts (CBC) and Hb S levels are also obtained. Hb S is quantitated by high-performance liquid chromatography (HPLC) [12].

RESULTS

Patients on pheresis were compared to their previous experience with simple/partial transfusion for complications, efficacy, blood utilization, cost, and iron load. (Some patients began pheresis on a Haemonetics machine [Braintree, MA]. For this report, results are from the period of time when all patients were pheresed in the same manner with a COBE® Spectra™ machine. Note total duration of pheresis vs. observation period in

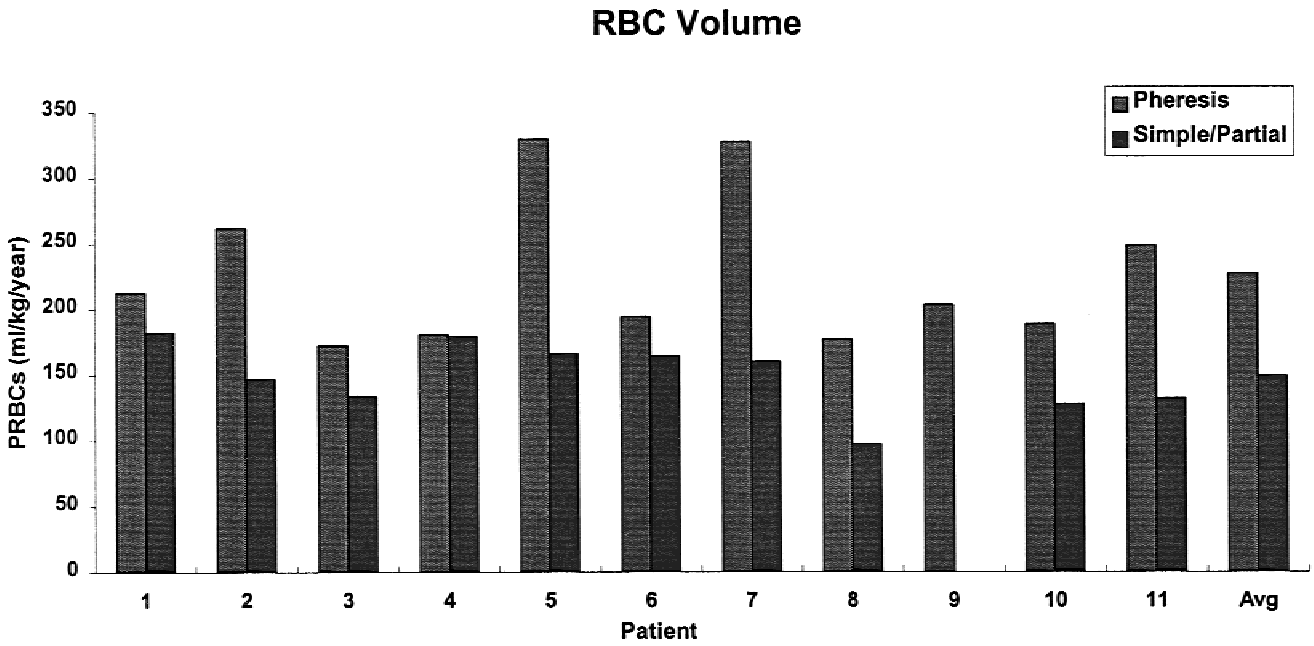

Fig. 1. Comparison of RBC volume (ml/kg/per year) between patients' experiences on pheresis and their experiences on a simple transfusion program. Blood utilization for the group increased by an average of 52%.

Table I.) No patient has experienced any significant complications on pheresis although three patients had occasional problems with venous access. No patient has had a recurrent stroke with mean pre-pheresis Hb S levels of 44%. (Mean pre-pheresis Hb S level represents the average pre-pheresis value for patients once stable Hb S levels were achieved.) Note that five patients averaged pre-pheresis Hb S levels ⩾50%, but only one patient was significantly higher at 55.9%. (Table I summarizes clinical features and mean laboratory values.)

Consistent with previous reports [10,11], erythrocytapheresis significantly increased blood utilization. Figure 1 shows the amount of PRBCs used in ml/kg per year for each patient on pheresis compared with the amount of PRBCs used in a year of simple/partial transfusion. Blood utilization increased by an average of 52% for the group. As expected, donor exposure (Fig. 2) increased in all except patients 4 and 6, who required frequent partial exchange transfusions prior to pheresis. Despite the increase in blood utilization and donor exposure, no patient developed an alloantibody or any infectious complications (Hepatitis B, C, or HIV).

Figures 3–5 show the effect of pheresis on ferritin levels in representative patients with different chelation statuses. Pheresis patients were divided into three groups as previously designated by Adams et al. [11]: 1) Patients with significant pre-pheresis iron load continued on chelation; 2) Patients with significant iron load not chelated; and 3) Patients started on pheresis prior to development of significant iron load. Patients switched from simple transfusion to pheresis who continued deferoxamine (Fig. 3), with serum ferritin levels >5,000 ng/ml stabilized, but did not decrease significantly—a different outcome than previously reported for chelated patients with significant pre-pheresis iron load [11]. In contrast, patient 6, with a pre-pheresis ferritin level <5,000 ng/ml had a gradual decline in ferritin levels with the switch to pheresis and maintenance of chelation.

Figure 4 represents ferritin levels in non-chelated patients. Both patients began pheresis with ferritin levels <5,000 ng/ml are both maintained stable iron load as measured by serum ferritin while pheresed with no chelation. To date, however, no decrease in ferritin has occurred for these patients.

The most dramatic effect of pheresis on ferritin levels was seen in patient 8 who began pheresis less than a year into a traditional transfusion protocol. As shown in Figure 5, she has maintained ferritin levels between 50–200 ng/ml for over 2½ years on pheresis without initiating chelation. Included for comparison are serum ferritin levels of a patient who started a simple transfusion program five days prior to initiation of pheresis in patient 8.

Cost analysis was performed by comparing the average annual cost of one year of pheresis with the annual cost of simple transfusion. As noted in Table I, patients on pheresis have a visit interval of 35.1 days or an average of 10 phereses per year. The patients' previous experiences with simple transfusion required visits every 29.6 days or 12 visits per year. Although pheresis pa-

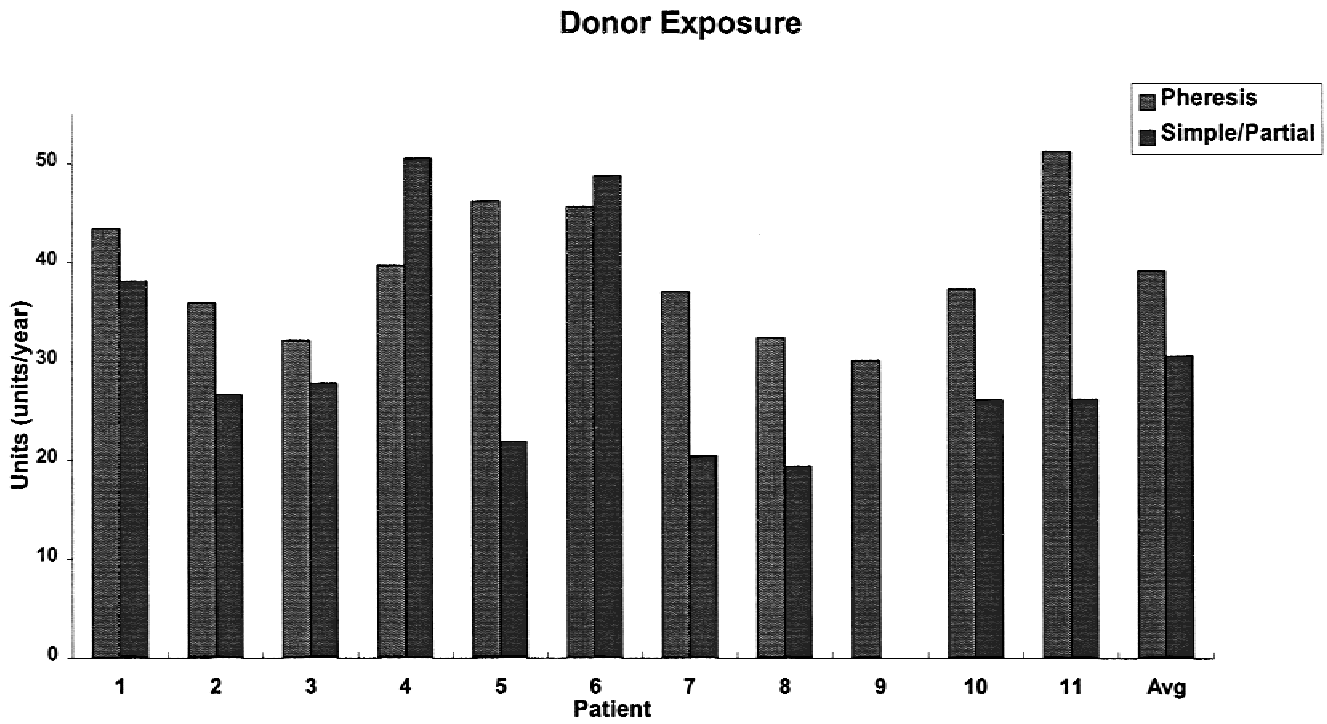

Fig. 2. Comparison of donor exposure (units/year) between patients' experiences on pheresis and their experiences on a simple transfusion program. Donor exposure increased for all except patients 4 and 6 who required frequent partial exchange transfusions to adequately control Hb S prior to the switch to pheresis.

tients require fewer treatments per year, the average annual charge for pheresis (lab, blood bank fees, and pheresis charge) is $36,085 compared with $26,058 for simple transfusion. However, if the cost of chelation ($29,480 per year for medication, supplies, and home health fees) is added to simple transfusion, pheresis without chelation is less expensive than simple transfusion programs.

DISCUSSION

Iron overload remains the most significant problem for sickle cell patients on chronic transfusion programs. Although deferoxamine provides effective chelation, many chronic transfusion patients are not compliant with daily subcutaneous infusions, and to date, no other chelators are licensed for use. Two recent reports evaluated erythrocytapheresis as an alternative method for controlling iron accumulation in chronically transfused sickle cell patients [10,11]. These studies showed stabilization of iron load as measured by serum ferritin, and, in some patients, ferritin actually decreased despite a net positive annual RBC load.

Our experience to date with pheresis for chronically transfused sickle cell patients differs slightly as to effect on iron status. Nine of the 11 patients in our program have undergone pheresis for a minimum of 12 months with an average time on pheresis of 19 months (range 4–36 months). Of the patients continued on chelation during pheresis, those with pre-pheresis serum ferritin levels >5,000 ng/ml stabilized, but did not have the dramatic decrease in iron load reported by Adams and colleagues [11]. The one chelated patient with ferritin level <5,000 ng/ml pre-pheresis decreased significantly with his latest ferritin level at 1,500 ng/ml. However, no patient on chelation has yet experienced a change in iron status significant enough to discontinue deferoxamine.

The effect of pheresis on the iron status of non-chelated patients in our population also varies from that of Adams et al. [11], who reported one of four non-chelated patients, with a pre-pheresis ferritin level >8,000 ng/ml, decreased to 4,000 ng/ml in less than two years of pheresis. In our experience, non-chelated patients with pre-pheresis ferritin levels <5,000 ng/ml maintained stable ferritin levels on pheresis, but thus far show no trend toward lower iron load as measured by serum ferritin.

One explanation for these differences is the lack of an accurate, inexpensive, and non-invasive method of monitoring iron load. Because factors other than iron status affect serum ferritin, its usefulness as a predictor of body iron stores is limited [13–15], particularly for patients with ferritin concentrations over 4,000 μg/L (16). It is also possible that our patients judged compliant with deferoxamine are actually not, or that some difference in

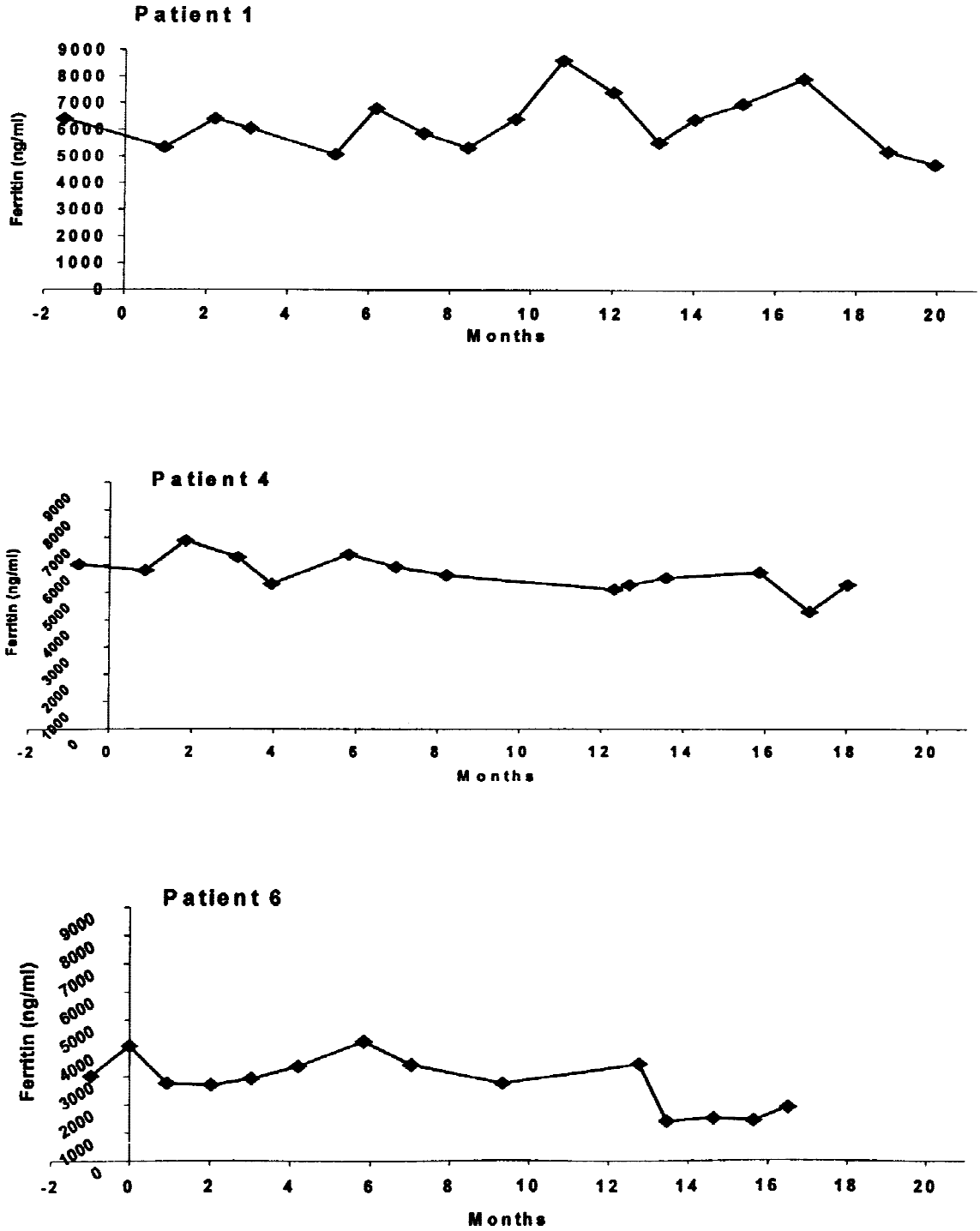

Fig. 3. Ferritin values (ng/ml) in chelated pheresis patients. Pheresis started at month 0. The last ferritin level on simple transfusion is also shown. Although levels fluctuate, chelated patients with pre-pheresis ferritin level >5000 ng/ml showed an overall stabilization compared with their increasing ferritin values on simple transfusion. Note that patient 6, with a pre-pheresis level <5,000 ng/ml, shows a gradual decrease in ferritin levels on pheresis.

technique of pheresis accounts for the different outcome. The initial study of pheresis for chronically transfused sickle cell patients [10] used a Haemonetics system, but the subsequent report of Adams et al. [11] used the same COBE® Spectra™ processor in use at our facility.

Our work does reinforce the previous finding [10,11] that pheresis is most effective at iron control if initiated early in the course of a transfusion program. As shown in Figure 5, patient 8 started pheresis with a serum ferritin level of 500 ng/ml and has maintained ferritin levels

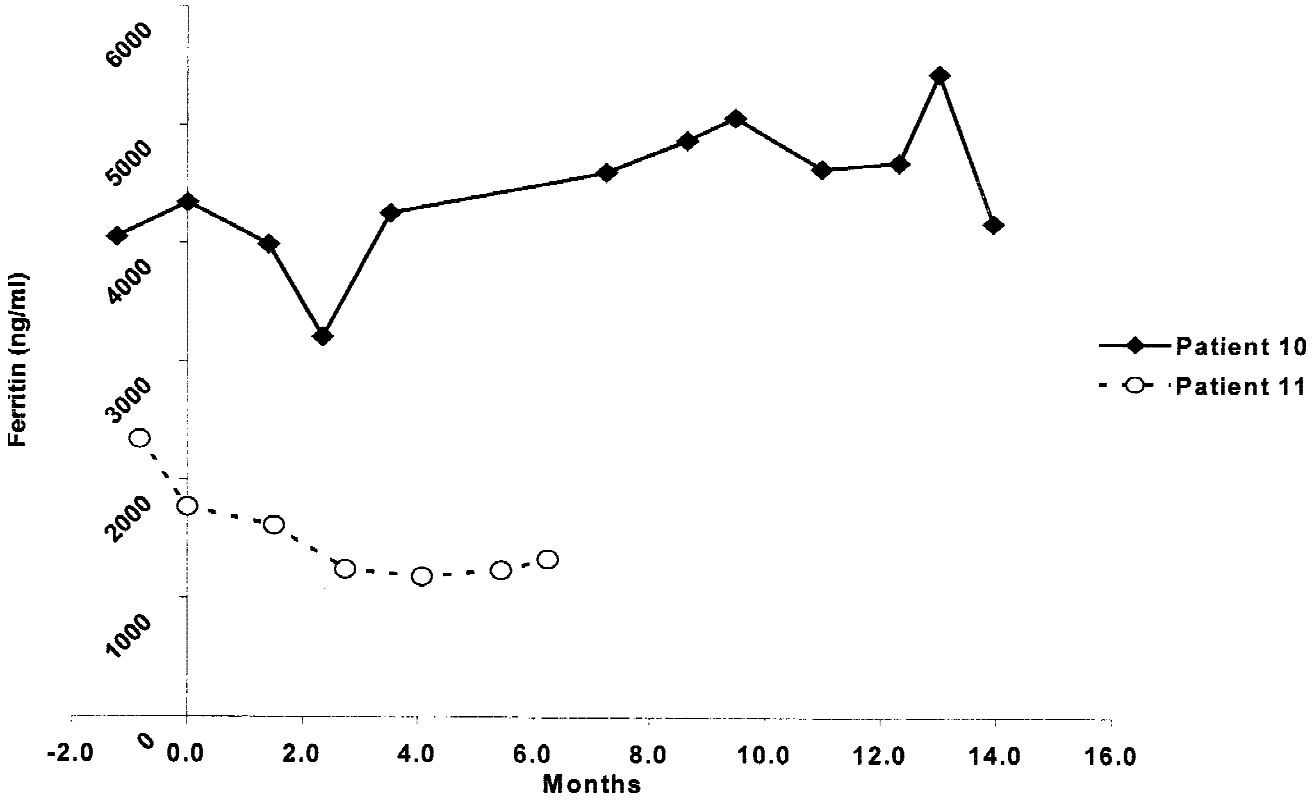

Fig. 4. Ferritin levels (ng/ml) in non-chelated pheresis patients. Pheresis started at month 0. The last ferritin level on simple transfusion is also shown. Both patients had ferritin levels <5,000 ng/ml at initiation of pheresis and both remained stable without chelation.

<200 ng/ml without chelation for over 30 months of treatment—an outcome not attainable with simple transfusion programs.

To summarize, for our patient group, the effect of pheresis on iron load is determined by pre-pheresis iron load and chelation status. Chelated patients with serum ferritin levels less than 5,000 ng/ml at the beginning of pheresis have decreased ferritin levels on pheresis. Chelated patients with higher pre-pheresis iron loads, as well as non-chelated patients with lower iron load (ferritin levels <5,000 ng/ml), have the same response—stabilization of ferritin compared with their prior experiences on simple transfusion, but no significant decreases. Our experience to date shows that pheresis should start as soon as adequate venous access is possible, but certainly before ferritin levels exceed 5,000 ng/ml or earlier if the patient cannot or will not use deferoxamine.

Consistent with prior reports, erythrocytapheresis increases blood utilization [10,11]. To date, no patients on the pheresis program have developed any new alloantibodies or infectious complications. However, the study size and length of observation are not long enough to definitively conclude that complications will not occur.

Likewise, the safety of higher Hb S levels (mean of 44% with one patient significantly greater than 50%) is not clear. As patients were changed from simple transfusion to pheresis, it became clear that to never exceed 50% pre-pheresis Hb S would require more frequent pheresis or a further increase in blood utilization. (Longer periods between phereses decreased problems with venous access.) Therefore, we tolerated pre-pheresis Hb S levels slightly >50%. Our results support previous experience that higher Hb S levels are tolerated without recurrent neurological events [17,18]. In fact, pheresis may be a safer means of allowing higher Hb S levels because the post-transfusion hematocrit is controlled so accurately with pheresis. Thus, patients are less likely to experience increased viscosity with hematocrits greater than 35% in the face of higher Hb S levels.

With limited health care resources, it is important to consider the cost and accessibility of new therapies. Pheresis is significantly more expensive than simple transfusion and is not available at all hospitals. One patient who was previously transfused in her community now travels to our tertiary care center for pheresis. However, if chelation can be avoided as in patient 8, pheresis decreases cost as well as improves quality of life for chronically transfused sickle cell patients.

In conclusion, pheresis is an effective means of maintaining Hb S levels in chronically transfused sickle cell

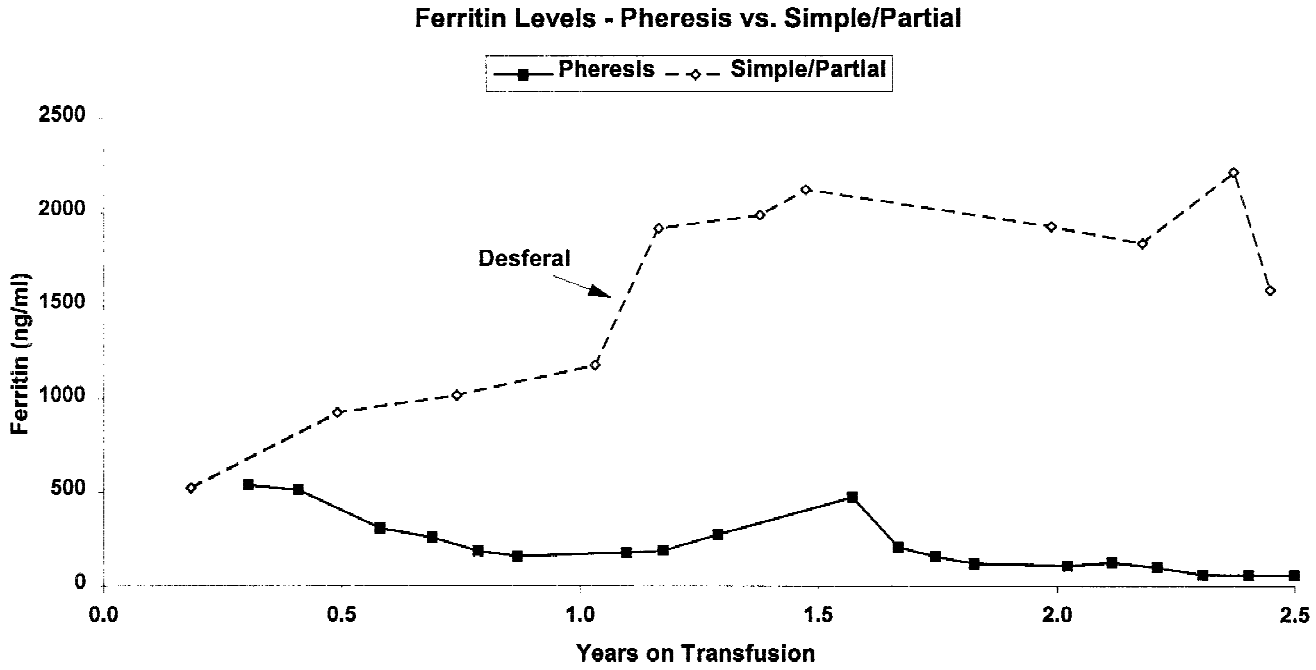

Fig. 5. Comparison of ferritin values for a patient who began simple transfusion (dashed line) five days before patient 8 started pheresis. Patient 8 has maintained normal ferritin values for 30 months on pheresis and has not required chelation.

patients. The most productive use of this therapy is early in the course of chronic transfusion, before significant iron load has developed. Although smaller patients are pheresed, the procedure is still technically difficult in younger patients due to venous access. Sickle cell patients now represent the largest chronic transfusion group in the United States [19], and the majority of these transfusions are performed because of cerebrovascular accidents, a complication which occurs most frequently in the first decade of life. The number of chronically transfused patients will continue to increase if transfusion remains the only effective therapy for stroke. Pheresis is a promising alternative which requires further development to consistently allow its use in younger patients who will benefit the most from this therapy.

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